PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY



To:
G. E. EHRLICH (1995) LTD.
11 MENACHEM BEGIN STREET
RAMAT GAN, ISRAEL 52 521

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

| | |
|---|---|
| Applicant's or agent's file reference<br>27040 | Date of mailing (*day/month/year*) 15 APR 2005<br>FOR FURTHER ACTION<br>See paragraph 2 below |

| International application No. | International filing date (*day/month/year*) | Priority date (*day/month/year*) |
|---|---|---|
| PCT/IL04/00275 | 25 March 2004 (25.03.2004) | 26 March 2003 (26.03.2003) |

International Patent Classification (IPC) or both national classification and IPC

IPC(7): C07K 16/00; G01N 33/53; A61K 39/395 and US Cl.: 530/387.1, 387.3, ; 435/7.1 ; 424/130.1, 133.1, 178.1

Applicant

TECHNION RESEARCH & DEVELOPMENT FOUNDATION LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
Valerie Bell-Harris
Zachariah Lucas

Telephone No. 571-272-1600

Form PCT/ISA/237 (cover sheet) (January 2004)

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IL04/00275

**Box No. I Basis of this opinion**

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☒ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☒ in written format

☒ in computer readable form

c. time of filing/furnishing

☒ contained in international application as filed.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IL04/00275

**Box No. IV Lack of unity of invention**

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has:
   - ☐ paid additional fees
   - ☐ paid additional fees under protest
   - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   - ☐ complied with
   - ☒ not complied with for the following reasons:

   See the lack of unity section of the International Search Report(Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☐ all parts.
   - ☒ the parts relating to claims Nos. 1-9, 14-35, 40-52, 101-106, 109-126, 129-140, 176-179, 181-195 (species = SEQ ID NO: 14)

Form PCT/ISA/237 (Box No. IV) (January 2004)

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IL04/00275

**Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | |
|---|---|---|
| Novelty (N) | Claims Please See Continuation Sheet | YES |
| | Claims Please See Continuation Sheet | NO |
| Inventive step (IS) | Claims Please See Continuation Sheet | YES |
| | Claims Please See Continuation Sheet | NO |
| Industrial applicability (IA) | Claims Please See Continuation Sheet | YES |
| | Claims Please See Continuation Sheet | NO |

2. Citations and explanations:

Please See Continuation Sheet

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IL04/00275

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V.1. Reasoned Statements:
The opinion as to Novelty was positive (Yes)with respect to claims 5, 18, 22, 25, 27-35, 40-52,101-106, 109-126,129-140,176-179,181-187, 189-195
The opinion as to Novelty was negative (No) with respect to claims 1-4,8-9, 14-17, 19-21, 23, 24, 26
The opinion as to Inventive Step was positive (Yes)with respect to claims 5,31, 110, 130, 178, 188
The opinion as to Inventive Step was negative(NO) with respect to claims 1-4, 6-9, 14-30, 32-35, 40-52, 101-106, 109, 111-126, 129, 131-140, 176-179, 181-187, 189-195
The opinion as to Industrial Applicability was positive (YES) with respect to claims 1-9, 14-35, 40-52, 101-106, 109-126, 129-140, 176-179, 181-195
The opinion as to Industrial Applicability was negative(NO) with respect to claims NONE

V. 2. Citations and Explanations:

Claims 1, 3, 4, 8, 16, 17, 19, 20, 23, and 24 lack novelty under PCT Article 33(2) as being anticipated by Andersen et al. (PNAS 93: 1820-24). These claims describe compositions comprising antibodies with specificity towards complexes of antigen-presenting molecules and pathogen derived antigens. The Andersen reference discloses such an antibody. See e.g., pages 1820-21. The reference therefore anticipates the indicated claims.

Claims 1, 3, 4, 8-9, 14-17, 19, 20, 23, 24, and 26 lack novelty under PCT Article 33(2) as being anticipated by Reiter et al. (PNAS 94: 4631-36). These claims describe compositions comprising antibodies with specificity towards complexes of antigen-presenting molecules and pathogen derived antigens, including embodiments wherein the antigen is a viral antigen, and the antibody is further attached to a toxin. Such an antibody is disclosed in the Reiter reference. See e.g., abstract, and page 4631. The reference therefore anticipates the indicated claims.

Claims 1, 2, 8, 16, 17, 19, 20, 21, 24, and 26 lack novelty under PCT Article 33(2) as being anticipated by Polakova et al., J Immunol 165: 5703-12. These claims read on compositions comprising a monoclonal antibody with specificity towards complexes of class I antigen-presenting molecules and retroviral antigens. Such antibodies are disclosed by the reference. See, page 5704. The reference therefore anticipates the indicated claims.

Claims 1 and 16-19 lack an inventive step under PCT Article 33(3) as being obvious over over Reiter et al. (supra.). Claims 16-19 read on the composition of claim 1, wherein the antigen-presenting molecule is an HLA-A2 molecule. The teachings of Reiter have been described in part above. The reference additionally teaches that certain human diseases are associated with antigen peptides that form complexes with claims 1 HLA-A2 molecules, and suggests the identification of antibodies that target such antigen/HLA-A2 complexes for use in the disclosed antibody/toxin conjugate. The reference therefore renders obvious the claimed methods.

Claims 2-4, 6, and 7 lack an inventive step under PCT Article 33(3) as being obvious over either of Reiter or Andersen as applied to claim 1 above, and further in view of the teachings of Theodore (U.S. 6,416,738). The indicated claims describe embodiments of the claimed compositions comprising monoclonal antibodies, humanized antibodies, or binding fragments of any antibody with the indicated binding specificity. The art indicates that such forms of antibodies are each recognized in the art as functional equivalents, and that the making of such different antibody forms is known. See e.g., Theodore et al., column 11 lines 14-50, and col. 58 lines 38-63. Because the art indicates that these antibodies, or antibody-derived molecules, are functional equivalents, it would have been obvious to those in the art to make or use any of these types of molecules in the claimed compositions.

Claims 1, 3, 4, 8-9, and 14-17, and 19-24 lack an inventive step under PCT Article 33(3) as being obvious over Reiter as applied to claims 1, 3, 4, 8-9, 14-17, 19, 20, 23, and 24 above, and further in view of Engberg et al. (Immunotechnology 4(3-4): 273-78) and Matsushita et al. (U.S. 5,591,829). These claims read on the claimed compositions wherein the antigen is an antigen of the human T lymphotrophic virus-1 (HTLV-1). The teachings of Reiter have been described above. As indicated above, the reference suggests the

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

identification of antibodies against complexes of a pathogen antigen and antigen-presenting molecules, and the incorporation of such antibodies into antibody/toxin conjugates for use in the killing of pathogen infected cells. However, the reference does not specifically suggest the use of such compounds for the treatment of HLTLV-1 infections.
The suggestion for such a modification of the antibody/toxin conjugates of Reiter may be found in the teachings of Matsushita and Engberg. Engberg suggests the use of antibodies such as those described in Reiter for the treatment of diseases, including viral infection, through the mechanism suggested in Reiter. Matsushita suggests the use of antibodies attached to toxins for the treatment of HTLV-1 infections. Column 1, lines 18-36. From the teachings and suggestions of these references, and the teachings in Reiter that the conjugates disclosed therein were effective in killing virus-infected cells, it would have been obvious to those in the art to make and use such conjugates for the killing of HTLV-1 infected cells. The references therefore render the claimed methods obvious.

Claims 1, 3, 4, 8-9, and 14-25 lack an inventive step under PCT Article 33(3) as being obvious over Reiter in view of Engberg and Matsushita as applied against claims 1, 3, 4, 8-9, and 14-24 above, and further in view of the teachings of Saito et al. (J Virol 75(2): 1065-70). Claims 18 and 25 further limits the composition described above to embodiments wherein the antigen-presenting molecule is an HLA-A2 molecule and the antigen is a portion of a Tax protein. The teachings of Reiter, Engberg, and Matsushita have been described above. However, while these references suggest the targeting of the described antibody/toxin conjugates against HTLV-1 infected cells, the references do not specify and particular antigen-presenting molecule/antigen complex to be targeted.

The teachings of each of Saito indicate that a peptide of the HTLV-1 Tax protein is attached to the HLA-A2 antigen-presenting protein in HLTV-1 infected cells. Page 1065. In view of these teachings, it would have been obvious to those in the art to use target this antigen-presenting protein/antigen complex as a target for the antibody/toxin conjugates suggested by the Reiter, Engberg, and Matsushita. Those in the art would have had a reasonable expectation of success in the making of, and killing of HTLV-1 infected cells with, these conjugates in view of the suggestion in the references that the conjugates would be useful for the killing of HTLV-1 infected cells, and the demonstration in Reiter that similar conjugates were effective in killing cells infected by another virus. The references therefore render the indicated claims obvious.

Claims 27-30, 32-35, 40-43, 45, 46, 49, 50, and 51 lack an inventive step under PCT Article 33(3) as being obvious over Reiter as applied to claims 1-4, 6-9, 14-17, 19, 20, 23, 24, and 26 above, and further in view of Theodore as applied (in part) above, and Lawson et al. (U.S. 5,952,471). These claims describe compositions such as those in the previously described claims, but further require that the antibodies (or fragments thereof) be in multimeric form. The teachings of Reiter have also been described above. While the reference refers to antibodies generally, the example provided in the reference is a Fab fragment, and the reference does not teach or suggest the use of multimeric forms of the antibodies.
The Theodore et al. reference also has been described above. As was indicated above, the reference indicates that the several forms of antibodies identified in the previous claims are equivalents to each other. The reference also suggests the making of multimeric forms of such antibodies or fragments. See e.g., col. 59. This suggestion that multimeric forms of antibodies are a recognized equivalent is supported by the teachings of Lawson. Col 3, lines 4-11 (teachings that multimeric forms of monospecific antibodies or fragments thereof may be used as an equivalent of antibodies or fragments thereof). In view of these teachings, it would have been obvious to those in the art to use such multimeric antibodies or antibody fragments as the targeting domain in the conjugates suggested by Reiter. The references therefore render the claims obvious.

Claims 27-32, 34, 35, 40-52 51 lack an inventive step under PCT Article 33(3) as being obvious over Reiter in view of Engberg, Matsushita, and Saito as applied to claims 1, 3, 4, 8-9, and 14-25 above, and further in view of Theodore, and Lawson as applied against (e.g.) claims 27-30, 32-35, 40-43, 45, 46, 49, 50, and 51 above. These claims read on embodiments of the claimed invention wherein the antigen-presenting molecule is an HLA-A2 molecule and the antigen is an HTLV-1 antigen comprising a portion of a Tax protein. The teachings of the various references have been described above. As indicated above, the teachings of Reiter, Engberg, Matsushita, and Saito teach or suggest the limitations of the rejected claims, except that they do not, alone, teach or suggest the use of the various antibodies or fragments of the claims in multimeric form. However, the teachings of the later references both suggest the use of other antibody molecules, and the use of multimeric forms thereof. The combined teachings of the references therefore render obvious the use of multimeric forms of the antibodies or fragments thereof in the antibody/toxin conjugates suggested by the first four references. The claims are therefore obvious over the indicated art.

Claims 101-106, 109, 111-123, 125, 126, 129, 131-140 lack an inventive step under PCT Article 33(3) as being obvious over Andersen as described above in view of Reiter, or Reiter in view of Engberg, Matsushita, and Saito as applied above. These claims read on methods of detecting (or diagnosing an infection based on the detection of) an antigen-presenting portion of a complex comprising an antigen-presenting molecule and an antigen using the antibodies of claim 1. The teachings of Andersen and of Reiter etc. have been described, at least in part, above. Andersen additionally teaches that such antibodies may be used in methods for the detection of T-cell epitopes, and the expression of T-cell epitopes on antigen presenting cells. The refernece also suggests the use of such antibodies as diagnositics for the detction of intracellular pathogens based on the expression of antigens for those pathogens on and MHC complex. Page 1824. From these teachings, it would have been obvious to those in the art that any of the antibodies suggested by the references could be used in such diagnostic methods. The combined teachings of these references therefore renders the claimed inventions obvious.

Claim 124 lacks an inventive step under PCT Article 33(3) as being obvious over Andersen in view of Lawson. This claim reads on the method of claim 101 wherein the antibody used to detect the complex is administered to an individual. The teachings of Andersen have been described above. While the reference teaches the use of the antibodies to detect the indicated complexes, the reference does not

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

teach or suggest the administration of antibodies to an individual for diagnostic purposes. However, such a method is taught by Lawson. Columns 3-4. Because Lawson teaches that antibodies may be administered to a subject for use in detecting targets of the antibody, and because Andersen teaches the use of the claimed antibodies for diagnostic purposes, it would have been obvious to those in the art to use the antibodies of Andersen in the methods of Lawson. The references therefore render the claimed method obvious.

Claims 176-179, 181-187, and 189-195 lack an inventive step under PCT Article 33(3) as being obvious over Stewart et al. (U.S. 5,695,928) in view of Andersen, Reiter, Engberg, Matsushita, and Saito as described above. These claims read on methods of detecting a complex of a antigen-presenting molecule and an antigen in a sample through attaching the sample to the surface, and using the antibodies described above to detect the complexes, if any, in the sample. Stewart teaches immunoassays for the detection of targets of antibodies, including embodiments wherein the sample is bound to a solid support for detection with a labeled antibody. Column 2. Because the Stewart references teaches methods of detection using antibodies, and the other references render obvious the use of the claimed antibodies in detection methods, the combined teachings of the references render the claimed methods obvious.